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CHARLES S. JULIARD, Captain, USAAC
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cyclodecapentaen

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INVESTIGATIONS BY PROFESSOR KUHN KAISER WILHELM INSTITUT FUR MEDIZINISCHE FORSCHUNG

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FURTHER DATA ON SALICIL AND
INVESTIGATIONS BY PROFESSOR RICHARD KUHN,
KAISER WILHELM INSTITUT FUR MEDIZINISCHE FORSCHUNG
HEIDELBERG

29 May 1945

Reported By

ERNEST H. VOLWILER, U.S. Civilian

CIOS Target Number 24/17 (a)
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COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE
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Personnel of Team.
Ernest H. Volwiler, U.S. Civilian.

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Professor Kuhn was visited for additional questioning regarding his work on biological and medical problems. He was very cooperative and freely discussed his research work of the past few years.

Cyclodecapentaene.

Prof Kuhn received his first sample, presumably $C_{12}H_{12}$, from Dr. Reppe about a year ago. It had an inky-blue color, reminiscent of the azulenes obtained from the camomiles, and the absorption spectra were also similar. The azulenes have 5- and 7-carbon ring structures with conjugated double bonds, and are related to the terpenes. The camomiles have long been used for treating inflammatory processes, which suggested similar trials with cyclodecapentaene and its homologs.

The known and closely related cyclo-octatetrene had been found toxic and not very active against the B. coli group. Cyclodecapentaene, on the other hand, was not toxic to rats, in 0.5 to 1 gram doses, given subcutaneously. Kuhn did not have readily available the detailed bacteriological results from the use of this compound, but agreed to send them through military channels.

The second potential use for this compound was based on the known slight effect of the azulenes in minimizing mustard gas burns. Since the compound in question has a similar conjugated structure, it was tried, first in rats and then by Kuhn and his students on their own skin. Kuhn stated that even as long as two hours after application of mustard gas, protection against severe burns was afforded. Of course, during the intervening period some tissue damage will already have occurred, but the compound greatly decreases subsequent inflammation. When the product was used as an antidote for mustard gas, only the first skin reactions were produced; the secondary inflammatory reactions were prevented. For such use, Kuhn does not believe that the conjugated double-bond structure is particularly necessary; in fact, a compound with the structure $-C=C=C-$ may be preferable. However, Kuhn has no more of the Reppe compound to continue his work. His attention was called to Reppe's statement that there was some confusion as to the nature of the compound which Kuhn actually had, but Kuhn had no explanation of this.

Vitamin Research

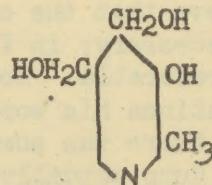
(1) Vitamin A has not been studied recently, except in relation to the supply and stabilization of carotenes. In reply to an inquiry as to the published synthesis of Vitamin A reported about 1937 by Kuhn and his student C.L.D. Morris (of London), Kuhn stated that the biological activity tests had been made by the I.G. at Elberfeld, and reported to be 750 "cod-liver oil units",

indicating a Vitamin A purity of 7.5 per cent. Later Michel, working in Kuhn's laboratory, tried to duplicate Morris' synthesis, and although he obtained some activity, it was of a definitely lower order.

(2) Vitamin E during the last few years has had considerable attention in this laboratory. In doses much larger than normal, it was found to prevent and cure fatty degeneration of the liver in rats which had been fed an E-deficient diet. However, this diet contained sufficient E to permit reproduction, but not enough to prevent liver damage. Such rats regularly die in 35 to 45 days, but if given large doses of E (130 gammas per rat per day of synthetic d-l- α -tocopherol acetate), the fatty degeneration disappears as can be shown histologically. The amounts of Vitamin E required for the Evans test are not sufficient to prevent such liver damage. These results were published by Klaus Schwarz in Hoppe-Seyler's Zeit für physiol. Chem. 281: 101, 109 (1944). These observations may indicate a use in the treatment of poisoning by phosphorus, chlorinated hydrocarbons, and poisonous mushrooms.

The above work has been under way for 4 years. Kuhn has done no synthetic work on tocopherol analogs. He stated that it has been customary in Germany to bleach flour with $NaCl_3$, which caused the loss of 80 percent of the E content of Germany's bread, or 30,000 kg. per year. Kuhn has long advocated the abandonment of the use of $NaCl_3$, and his recommendation was adopted just before the close of the war. Kuhn stated that Prof. Victor Grafe at Würzburg has the clinical results on E studies, and that he may be worth interrogating.

(3) Vitamin B₆ has also received attention. Based upon the observation that after B₆ administration a product much more potent is excreted in the urine, Kuhn isolated and characterized it. The compound is



It was isolated as the picrate. Kuhn stated that he had been informed that Snell at Wisconsin had independently made the same observation.

(4) Citrin has not been studied, but rutin, obtained from tobacco, has been investigated. It was found by Moewus at K.W.I. that rutin has a very pronounced action on the gametes of algae, by inhibiting the copulation of algae cells. This is a characteristic of the flavanols, and was referred to as the isorhamnatin

effect. It is due to the 3-methylether of Vueroetin. The test method is described by Franz Moewus, Jahrbücher für Wissenschaftliche Botanik 86: 753-83 (1938).

(5) Much work has also been done on vitamins as components of culture media for bacteria.

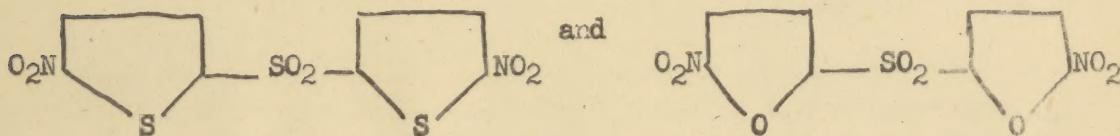
Dibromosalicil

Dibromosalicil was said to work well against Staph. albus infections, where penicillin is not very effective. It was stated to be 300 times as effective against albus as calcium penicillin in tablet form of English origin.

The I.G. Elberfeld supposedly made a few kilos of the compound; since the end of 1944, Kuhn's laboratory has made about 500 grams for clinical use. Kuhn stated that perhaps the compound works better in the presence of protein. Against various organisms, dibromo-, tetrabromo-, dichloro-, or tetrachloro-, or other derivatives may exert specific actions. Weese at Elberfeld had not yet obtained the pure iod compound. The dinitro gave a good effect in vitro, but failed in vivo. An article has been submitted to the Berichte. They have not yet introduced alkyl or alkylamino groups in the ring.

Sulfones.

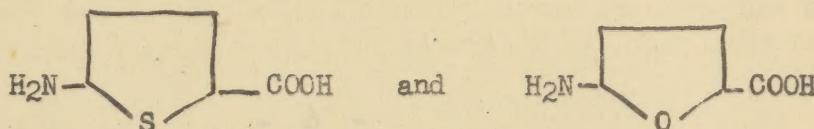
Kuhn has been studying compounds of the structure



They are more active than dibromosalicil in vitro, but fail in vivo. This work has been submitted to the Berichte.

Sulfonamide Antagonists.

Dr. Otto Dann in Kuhn's laboratory has made compounds similar to p-aminobenzoic acid:



These are much more unstable than PAB, and they do not act as antagonists as does PAB.

Local Anesthetics.

Kuhn's laboratories have also made the thiophene analog of procaine, but it is not a very good local anesthetic.

Proteolytic Enzymes.

From Prof. Schäffner at Waldschmidt-Leitz's laboratory in Prague, Kuhn received a proteolytic enzyme obtained from molds similar to Penicillium notatum. The enzyme remains on the mycelium; the liquid is simply decanted and the mycelium is dried with acetone, and tablets prepared therefrom. Kuhn stated that the product is $\frac{1}{2}$ as effective as the I.G. product "Festal", and much cheaper to prepare. The mold strain needed is not very specific, and Kuhn ventured the opinion that the enzyme might even be obtained as a by-product from penicillin manufacture. The product is used to aid in protein digestion.

Kuhn stated that this product, called "S-206", may also be useful, like other proteolytic enzymes, as a constituent of a cleaning preparation to remove spots from clothing, etc., and in the connection be referred to Rohm and Haas' proteolytic enzyme preparation.

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